label useful in such methods can be applied to the present invention. Particularly useful are enzymatically active groups, such as enzymes (see *Clin. Chem.*, 22:1243 (1976)), enzyme substrates (see British Pat. Spec. 1,548,741), coenzymes (see U.S. Pat. Nos. 4,230,797 and 4,238,565) and enzyme inhibitors (see U.S. Pat. No. 4,134,792); fluorescent markers (see Clin. Chem., 25:353 (1979); chromophores; luminescent compounds such as chemiluminescent and bioluminescent markers (see *Clin. Chem.*, 25:512 (1979)); specifically bindable ligands; proximal interacting pairs; and radioisotopes such as ^{3}H, ^{35}S, ^{32}P, ^{125}I and ^{14}C.

In similar fashion, anti-p16 antibodies can be labeled and used to detect the presence of p16 protein in samples of cells.

In yet another embodiment, the present invention particularly contemplates assays and kits for detecting p16 levels in cells. Antibodies specific for p16 (as described herein), or nucleic acid probes directed to detecting mRNA levels of p16 transcripts, can be used to detect transformed cells. As described above, the level of p16 mRNA, and presumably p16 protein, is elevated in transformed cells relative to normal cells. Thus, detecting the level of p16 gene expression is diagnostically useful in determining the presence of transformed cells.

On page 11, please replace the partial paragraph at the top of the page with:

sequence for a mouse p16/p15 clone is provided in SEQ ID No. 7. The corresponding amino acid sequences are represented in SEQ ID Nos. 2, 4, 6 and 8. An amino acid sequence for a partial human p16 is represented in SEQ ID No. 35. Moreover, data from hybridization and immunoprecipitation experiments indicates still other members of the CCR-protein family exist.

Please replace the abstract on page ~~83~~ 96 with:

The present invention relates to the discovery in eukaryotic cells, particularly mammalian cells, of a family of cell-cycle regulatory proteins ("CCR-proteins"). As described herein, this family of proteins includes a polypeptide having an apparent molecular weight of 16 kDa, and a

polypeptide having an apparent molecular weight of approximately 15 kDa, each of which can function as an inhibitor of cell-cycle progression, and therefore ultimately of cell growth. The present invention comprises antibodies directed to such CCR-proteins.

The paragraphs presented above incorporate changes as indicated by the marked-up versions below.

Cell-Cycle Regulatory Proteins, Antibodies and Uses Related Thereto

sequence for a mouse p16/p15 clone is provided in SEQ ID No. 7. The corresponding amino acid sequences are represented in SEQ ID Nos. 2, 4, 6 and 8. An amino acid sequence for a nearly complete human p16 is represented in SEQ ID No. 35. Moreover, data from hybridization and immunoprecipitation experiments indicates still other members of the CCR-protein family exist.

The present invention relates to the discovery in eukaryotic cells, particularly mammalian cells, of a ~~novel~~ family of cell-cycle regulatory proteins ("CCR-proteins"). As described herein, this family of proteins includes a polypeptide having an apparent molecular weight of 16 kDa, and a polypeptide having an apparent molecular weight of approximately 15 kDa, each of which can function as an inhibitor of cell-cycle progression, and therefore ultimately of cell growth. The present invention comprises antibodies directed to such CCR-proteins. ~~Thus, similar to the role of p21 to the p53 checkpoint, the subject CCR-proteins may function coordinately with the cell-cycle regulatory protein, retinoblastoma (RB). Furthermore, the CCR-protein family includes a protein having an apparent molecular weight of 13.5 kDa (hereinafter "p13.5"). The presumptive role of p13.5, like p16 and p15, is in the regulation of the cell-cycle~~.

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

Please cancel claims 59, 60, 65, 67, 71, 77, and 79-82 without prejudice.

I 5

11. (Amended) An antibody preparation specifically reactive with a 16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

I 6

58. (Amended) An isolated antibody, or fragment thereof, specifically immunoreactive with a 16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

I 7

61. (Amended) The antibody of claim 58, wherein the antibody is a monoclonal antibody.

62. (Reiterated) The antibody of claim 58, wherein the antibody is a Fab fragment.

N.E. (Duplicate)

63. (Reiterated) The antibody of claim 58, wherein the antibody is a $F(ab')_2$ fragment.

64. (Reiterated) The antibody of claim 58, wherein the antibody is labeled with a detectable label.

I 8

66. (Amended) A purified preparation of a polyclonal antibody, or fragment thereof, specifically immunoreactive with a 16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

I 9

68. (Amended) A kit for detecting a cell cycle regulatory (CCR) protein comprising (i) an isolated anti-CCR antibody, or fragment thereof, specifically immunoreactive with a ~~p~~16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, and (ii) means for detecting the anti-CCR antibody in immunocomplexes with a cell cycle regulatory (CCR) protein.

I 10

69. (Amended) The kit of claim 68, wherein the means for detecting the anti-CCR antibody is a detectable label conjugated with the anti-CCR antibody.

70. (Reiterated) The kit of claim 68, wherein means for detecting the anti-CCR antibody is a second antibody immunoreactive with the anti-CCR antibody.

72. (Reiterated) The kit of claim 68, wherein the antibody is a monoclonal antibody.

73. (Reiterated) The kit of claim 69, wherein the antibody is a purified preparation of polyclonal antibodies.

N.E. (Duplicate)

74. (Reiterated) The kit of claim 68, wherein the antibody is a Fab fragment.

75. (Reiterated) The kit of claim 68, wherein the antibody is a $F(ab')_2$ fragment.

76. (Reiterated) The kit of claim 68, wherein the antibody is provided in a form suitable for detecting the cell cycle regulatory (CCR) protein in samples in cells.

Please add the following new claims:

83. (New) An antibody preparation specifically reactive with a p16 protein having an amino acid sequence of SEQ ID No. 35.

84. (New) An isolated antibody, or fragment thereof, specifically immunoreactive with a p16 protein having an amino acid sequence of SEQ ID No. 35.

Add'l

85. (New) The antibody of claim 84, wherein the antibody is a monoclonal antibody.

86. (New) The antibody of claim 84, wherein the antibody is labeled with a detectable label.

87. (New) A kit for detecting a cell cycle regulatory (CCR) protein comprising (i) an isolated anti-CCR antibody, or fragment thereof, specifically immunoreactive with a p16 protein having an amino acid sequence of SEQ ID No. 35, and (ii) means for detecting the anti-CCR antibody in immunocomplexes with a cell cycle regulatory (CCR) protein.

88. (New) The kit of claim 87, wherein means for detecting the anti-CCR antibody is a detectable label conjugated with the anti-CCR antibody.

89. (New) The kit of claim 87, wherein the antibody is a monoclonal antibody.

90. (New) The kit of claim 87, wherein the antibody is provided in a form suitable for detecting the cell cycle regulatory (CCR) protein in samples in cells.

The claims presented above incorporate changes as indicated by the marked-up versions below.

11. (Amended) An antibody preparation specifically reactive with a ~~p~~16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody ~~specifically binds to a cyclin-dependent kinase (CDK)~~.

58. (Amended) An isolated antibody, or fragment thereof, specifically immunoreactive with a ~~p~~16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody ~~specifically binds to a cyclin-dependant kinase~~.

61. (Amended) The antibody of ~~any one of~~ claims 58~~, 59 or 60~~, wherein the antibody is a monoclonal antibody.

62. (Reiterated) The antibody of ~~any one of~~ claims 58, ~~59 or 60,~~ wherein the antibody is a Fab fragment.

63. (Reiterated) The antibody of ~~any one of~~ claims 58, ~~59 or 60,~~ wherein the antibody is a $F(ab')_2$ fragment.

64. (Reiterated) The antibody of claim 58, wherein the antibody is labeled with a detectable label.

66. (Amended) A purified preparation of a polyclonal antibody, or fragment thereof, specifically immunoreactive with a ~~p~~16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody ~~encoded by a nucleic acid that hybridizes at conditions of 2.0 x SSC at 50 °C or higher stringency to a nucleotide sequence of SEQ ID No. 1~~.

68. (Amended) A kit for detecting a cell cycle regulatory (CCR) protein comprising (i) an isolated anti-CCR antibody, or fragment thereof, specifically immunoreactive with a ~~p~~16 kD protein that coprecipitates with CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, and (ii) means ~~a detectable label~~ for detecting the anti-CCR antibody in immunocomplexes with a cell cycle regulatory (CCR) protein.

69. (Amended) The kit of claim 68, wherein the means for detecting the anti-CCR antibody is a detectable label conjugated with the anti-CCR antibody.

REMARKS

Claims 11, 58, 61-64, 66, 68-70, 72-76, and 83-90 constitute the pending claims in the present application. Applicant respectfully requests reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-4. Applicant notes that the CPA has been entered, the Examiner has changed, and that Applicant's amendments have been entered and arguments have been considered.

5-6. Applicant acknowledges the entry of the sequence listing, and points out that SEQ ID Nos. 15-17 are acknowledged where they first appear, on page 9, by the amendment filed on March 20, 2000. It is Applicant's understanding that such sequences need not be referenced each time they appear. Clarification is respectfully requested.

7. Applicant acknowledges the Examiner's indication of written support in priority application. Applicant will review this table for accuracy only to the extent necessary to secure